Heparin Structure and Interactions with Basic Fibroblast Growth Factor

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Crystal structures of heparin-derived tetra- and hexasaccharides complexed with basic fibroblast growth factor (bFGF) were determined at resolutions of 1.9 and 2.2 angstroms, respectively. The heparin structure may be approximated as a helical polymer with a disaccharide rotation of 174° and a translation of 8.6 angstroms along the helix axis. Both molecules bound similarly to a region of the bFGF surface containing residues asparagine-28, arginine-121, lysine-126, and glutamine-135; the hexasaccharide also interacted with an additional binding site formed by lysine-27, asparagine-102, and lysine-136. No significant conformational change in bFGF occurred upon heparin oligosaccharide binding, which suggests that heparin primarily serves to juxtapose components of the FGF signal transduction pathway.

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Amino acid sequence of bovine brain derived class 1 heparin-binding growth factor.

Strydom DJ, Harper JW, Lobb RR.

The major class 1 heparin-binding growth factor from bovine brain is a single-chain polypeptide of 140 amino acids with a molecular weight of 15 877. It has the amino acid sequence Phe1-Asn-Leu-Pro-Leu-Gly-Asn-Tyr-Lys-Lys-Pro-Lys-Leu-Leu- Tyr15-Cys-Ser- Asn-Gly-Gly-Tyr-Phe-Leu-Arg-Ile-Leu-Pro-Asp-Gly-Thr30-Val-Asp-Gly- Thr-Lys-Asp-Arg- Ser-Asp-Gln-His-Ile-Gln-Leu-Gln45-Leu-Cys-Ala-Glu-Ser-Ile-Gly- Glu-Val-Tyr-Ile- Lys-Ser-Thr-Glu60-Thr-Gly-Gln-Phe-Leu-Ala-Met-Asp-Thr-Asp-Gly-Leu-Leu-Tyr-Gly75- Ser-Gln-Thr-Pro-Asn-Glu-Glu-Cys-Leu-Phe-Leu-Glu-Arg-Leu- Glu90-Glu-Asn-His-Tyr- Asn-Thr-Tyr-Ile-Ser-Lys-Lys-His-Ala-Glu-Lys105-His-Trp-Phe-Val -Gly-Leu-Lys-Lys- Asn-Gly-Arg-Ser-Lys-Leu-Gly120-Pro-Arg-Thr-His-Phe-Gly-Gln-Lys -Ala-Ile-Leu-Phe-Leu-Pro-Leu135-Pro-Val-Ser-Ser-Asp140-OH. The mitogen is homologous to the class 2 heparin-binding growth factor pituitary fibroblast growth factor with about 50% of the amino acids being identical between the two mitogens.

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Differential effects of heparin, fibronectin, and laminin on the phosphorylation of basic fibroblast growth factor by protein kinase C and the catalytic subunit of protein kinase A.

Feige JJ, Bradley JD, Fryburg K, Farris J, Cousens LC, Barr PJ, Baird A.

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Basic fibroblast growth factor (FGF) is synthesized as a phosphoprotein by both bovine capillary endothelial and human hepatoma cells in culture. Because basic FGF is characterized by its high affinity for heparin and its association in vivo with the extracellular matrix, we examined the possibility that the phosphorylation of this growth factor by purified protein kinase C (PK-C) and the catalytic subunit of cAMP-dependent protein kinase-A (PK-A) can be modulated by components of the extracellular matrix. Heparin and other glycosaminoglycans (GAGs) inhibit the ability of PK-C to phosphorylate basic FGF. In contrast, heparin can directly increase the phosphorylation of basic FGF by PK-A. While fibronectin, laminin, and collagen IV have no effect on the ability of PK-C to phosphorylate basic FGF, they all can inhibit the effects of PK-A. Thus, there is a differential effect of extracellular matrix-derived proteins and GAGs on the phosphorylation of basic FGF. The enhanced phosphorylation of basic FGF that is mediated by heparin is associated with a change in the kinetics of the reaction and the identity of the amino acid targeted by this enzyme. The amino acids that are targeted by PK-C and PK-A have been identified by phosphopeptide analyses as Ser64 and Thr112, respectively. In the presence of heparin, basic FGF is no longer phosphorylated by PK-A at the usual PK-A consensus site (Thr112), but instead is phosphorylated at the canonical PK-C site (Ser64). Accordingly, heparin inhibits the phosphorylation of basic FGF by PK-C presumably by masking the PK-C dependent consensus sequence surrounding Ser64. Thus, when basic FGF is no longer phosphorylated by PK-A in the receptor binding domain (Thr112), it loses the increased receptor binding ability that characterizes PK-A phosphorylated basic FGF. The results presented here demonstrate three novel features of basic FGF. First, they identify a functional effect of the

binding of heparin to basic FGF. Second, they establish that the binding of heparin to basic FGF can induce structural changes that alter the substrate specificity of protein kinases. Third, and perhaps most important, the results demonstrate the existence of a novel interaction between basic FGF, fibronectin, and laminin. Although the physiological significance of this phosphorylation is not known, these results clearly suggest that the biological activities of basic FGF are regulated by a complex array of biochemical interactions with the proteins, proteoglycans, and glycosaminoglycans present in the extracellular milieu and the cytoplasm.

PMID: 2592418 [PubMed - indexed for MEDLINE]

1: J Cell Biochem 1993 Sep;53(1):74-84

Modulation of endothelial cell proliferation, adhesion, and motility by recombinant heparin-binding domain and synthetic peptides from the type I repeats of thrombospondin.

Vogel T, Guo NH, Krutzsch HC, Blake DA, Hartman J, Mendelovitz S, Panet A, Roberts DD.

Laboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892.

Thrombospondin is an inhibitor of angiogenesis that modulates endothelial cell adhesion, proliferation, and motility. Synthetic peptides from the second type I repeat of human thrombospondin containing the consensus sequence-Trp-Ser-Pro-Trp- and a recombinant heparin binding fragment from the amino-terminus of thrombospondin mimic several of the activities of the intact protein. The peptides and heparin-binding domain promote endothelial cell adhesion, inhibit endothelial cell chemotaxis to basic fibroblast growth factor (bFGF), and inhibit mitogenesis and proliferation of aortic and corneal endothelial cells. The peptides also inhibit heparin-dependent binding of bFGF to corneal endothelial cells. The antiproliferative activities of the peptides correlate with their ability to bind to heparin and to inhibit bFGF binding to heparin. Peptides containing amino acid substitutions that eliminate heparin-binding do not alter chemotaxis or proliferation of endothelial cells. Inhibition of proliferation by the peptide is time-dependent and reversible. Thus, the antiproliferative activities of the thrombospondin peptide and recombinant heparin-binding domain result at least in part from competition with heparin-dependent growth factors for binding to endothelial cell proteoglycans. These results suggest that both the Trp-Ser-Xaa-Trp sequences in the type I repeats and the amino-terminal domain play roles in the antiproliferative activity of thrombospondin.

PMID: 8227183 [PubMed - indexed for MEDLINE]

☐ 1: Structure 1997 Oct 15;5 (10):1325-38

The crystal structure of vascular endothelial growth factor (VEGF) refined to 1.93 A resolution: multiple copy flexibility and receptor binding.

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BACKGROUND: Vascular endothelial growth factor (VEGF) is an endothelial cell-specific angiogenic and vasculogenic mitogen. VEGF also plays a role in pathogenic vascularization which is associated with a number of clinical disorders, including cancer and rheumatoid arthritis. The development of VEGF antagonists, which prevent the interaction of VEGF with its receptor, may be important for the treatment of such disorders. VEGF is a homodimeric member of the cystine knot growth factor superfamily, showing greatest similarity to platelet-derived growth factor (PDGF). VEGF binds to two different tyrosine kinase receptors, kinase domain receptor (KDR) and Fms-like tyrosine kinase 1 (Flt-1), and a number of VEGF homologs are known with distinct patterns of specificity for these same receptors. The structure of VEGF will help define the location of the receptor-binding site, and shed light on the differences in specificity and cross-reactivity among the VEGF homologs. RESULTS: We have determined the crystal structure of the receptor-binding domain of VEGF at 1.93 A resolution in a triclinic space group containing eight monomers in the asymmetric unit. Superposition of the eight copies of VEGF shows that the beta-sheet core regions of the monomers are very similar, with slightly greater differences in most loop regions. For one loop, the different copies represent different snapshots of a concerted motion. Mutagenesis mapping shows that this loop is part of the receptor-binding site of VEGF. CONCLUSIONS: A comparison of the eight independent copies of VEGF in the asymmetric unit indicates the conformational space sampled by the protein in solution; the root mean square differences observed are similar to those seen in ensembles of the highest precision NMR structures. Mapping the receptor-binding determinants on a multiple sequence alignment of VEGF homologs, suggests the differences in

specificity towards KDR and Flt-1 may derive from both sequence variation and changes in the flexibility of binding loops. The structure can also be used to predict possible receptor-binding determinants for related cystine knot growth factors, such as PDGF.

PMID: 9351807 [PubMed - indexed for MEDLINE]

☐ 1: Proteins 1996 Nov;26 (3):353-7

Crystallization of the receptor binding domain of vascular endothelial growth factor.

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Vascular endothelial growth factor (VEGF) is a potent angiogenic factor with a unique specificity for vascular endothelial cells. In addition to its role in vasculogenesis and embryonic angiogenesis, VEGF is implicated in pathologic neovascularization associated with tumors and diabetic retinopathy. Four different constructs of a short variant of VEGF sufficient for receptor binding were overexpressed in Escherichia coli, refolded, purified, and crystallized in five different space groups. In order to facilitate the production of heavy atom derivatives, single cysteine mutants were designed based on the crystal structure of platelet-derived growth factor. A construct consisting of residues 8 to 109 was crystallized in space group P2 (1), with cell parameters a = 55.6 A, b = 60.4 A, c = 77.7 A, beta = 90.0 degrees, and four monomers in the asymmetric unit. Native and derivative data were collected for two of the cysteine mutants as well as for wild-type VEGF.

PMID: 8953654 [PubMed - indexed for MEDLINE]

☐ 1: J Biol Chem 1999 Feb 26;274(9):5612-9 Related Articles, NEW Books, LinkOut

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Vascular endothelial growth factor (VEGF) receptor II-derived peptides inhibit VEGF.

Piossek C, Schneider-Mergener J, Schirner M, Vakalopoulou E, Germeroth L, Thierauch KH.

JERINI BIO TOOLS GMBH, Rudower Chaussee 5, 12489 Berlin, Germany.

Vascular endothelial growth factor (VEGF) directly stimulates endothelial cell proliferation and migration via tyrosine kinase receptors of the split kinase domain family. It mediates vascular growth and angiogenesis in the embryo but also in the adult in a variety of physiological and pathological conditions. The potential binding site of VEGF with its receptor was identified using cellulose-bound overlapping peptides of the extracytosolic part of the human vascular endothelial growth factor receptor II (VEGFR II). Thus, a peptide originating from the third globular domain of the VEGFR II comprising residues 247RTELNVGIDFNWEYP261 was revealed as contiguous sequence stretch, which bound 125I-VEGF165. A systematic replacement with L-amino acids within the peptide representing the putative VEGF-binding site on VEGFR II indicates Asp255 as the hydrophilic key residue for binding. The dimerized peptide (RTELNVGIDFNWEYPAS)2K inhibits VEGF165 binding with an IC50 of 0.5 microM on extracellular VEGFR II fragments and 30 microM on human umbilical vein cells. VEGF165-stimulated autophosphorylation of VEGFR II as well as proliferation and migration of microvascular endothelial cells was inhibited by the monomeric peptide RTELNVGIDFNWEYPASK at a half-maximal concentration of 3-10, 0.1, and 0.1 microM, respectively. We conclude that transduction of the VEGF165 signal can be interrupted with a peptide derived from the third Ig-like domain of VEGFR II by blockade of VEGF165 binding to its receptor.

PMID: 10026178 [PubMed - indexed for MEDLINE]

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1: Biochemistry 1998 Dec 22;37 (51):17765-72

Crystal structure of the complex between VEGF and a receptor-blocking peptide.

Wiesmann C, Christinger HW, Cochran AG, Cunningham BC, Fairbrother WJ, Keenan CJ, Meng G, de Vos AM.

Department of Protein Engineering, Genentech, Inc., South San Francisco, California 94080, USA.

Vascular endothelial growth factor (VEGF) is a specific and potent angiogenic factor and, therefore, a prime therapeutic target for the development of antagonists for the treatment of cancer. As a first step toward this goal, phage display was used to generate peptides that bind to the receptor-binding domain (residues 8-109) of VEGF and compete with receptor [Fairbrother, W. J., Christinger, H. W., Cochran, A. G., Fuh, G., Keenan, C. J., Quan, C., Shriver, S. K., Tom, J. Y. K., Wells, J. A., and Cunningham, B. C. (1999) Biochemistry 38, 17754-17764]. The crystal structure of VEGF in complex with one of these peptides was solved and refined to a resolution of 1.9 A. The 20-mer peptide is unstructured in solution and adopts a largely extended conformation when bound to VEGF. Residues 3-8 form a beta-strand which pairs with strand beta6 of VEGF via six hydrogen bonds. The C-terminal four residues of the peptide point away from the growth factor, consistent with NMR data indicating that these residues are flexible in the complex in solution. In contrast, shortening the N-terminus of the peptide leads to decreased binding affinities. Truncation studies show that the peptide can be reduced to 14 residues with only moderate effect on binding affinity. However, because of the extended conformation and the scarcity of specific side-chain interactions with VEGF, the peptide is not a promising lead for small-molecule development. The interface between the peptide and VEGF contains a subset of the residues recognized by a neutralizing Fab fragment and overlaps partially with the binding site for the Flt-1 receptor. The location of the peptide-binding site and the hydrophilic character of the interactions with VEGF resemble more the binding mode of the Fab fragment than that of the receptor.

PMID: 9922142 [PubMed - indexed for MEDLINE]

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Novel peptides selected to bind vascular endothelial growth factor target the receptor-binding site.

Fairbrother WJ, Christinger HW, Cochran AG, Fuh G, Keenan CJ, Quan C, Shriver SK, Tom JY, Wells JA, Cunningham BC.

Department of Protein Engineering, Genentech, Inc., South San Francisco, California 94080, USA.

Peptides that inhibit binding of vascular endothelial growth factor (VEGF) to its receptors, KDR and Flt-1, have been produced using phage display. Libraries of short disulfide-constrained peptides yielded three distinct classes of peptides that bind to the receptor-binding domain of VEGF with micromolar affinities. The highest affinity peptide was also shown to antagonize VEGF-induced proliferation of primary human umbilical vascular endothelial cells. The peptides bind to a region of VEGF known to contain the contact surface for Flt-1 and the functional determinants for KDR binding. This suggests that the receptor-binding region of VEGF is a binding "hot spot" that is readily targeted by selected peptides and supports earlier assertions that phage-derived peptides frequently target protein-protein interaction sites. Such peptides may lead to the development of pharmacologically useful VEGF antagonists.

PMID: 9922141 [PubMed - indexed for MEDLINE]

☐ 1: A32398. basic fibroblast ...[gi:482272] BLink, OMIM, Related Sequences, PubMed, Taxonomy, LinkOut

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REFERENCE   1  (residues 1 to 210)
  AUTHORS   Gimenez-Gallego,G., Conn,G., Hatcher,V.B. and Thomas,K.A.
  TITLE     Human brain-derived acidic and basic fibroblast growth factors:
            amino terminal sequences and specific mitogenic activities
  JOURNAL   Biochem. Biophys. Res. Commun. 135 (2), 541-548 (1986)
  MEDLINE   86186784
REFERENCE   2  (residues 1 to 210)
  AUTHORS   Gautschi,P., Frater-Schroder,M. and Bohlen,P.
  TITLE     Partial molecular characterization of endothelial cell mitogens
            from human brain: acidic and basic fibroblast growth factors
  JOURNAL   FEBS Lett. 204 (2), 203-207 (1986)
  MEDLINE   86275260
REFERENCE   3  (residues 1 to 210)
  AUTHORS   Abraham,J.A., Whang,J.L., Tumolo,A., Mergia,A., Friedman,J.,
            Gospodarowicz,D. and Fiddes,J.C.
  TITLE     Human basic fibroblast growth factor: nucleotide sequence and
            genomic organization
  JOURNAL   EMBO J. 5 (10), 2523-2528 (1986)
  MEDLINE   87053817
REFERENCE   4  (residues 1 to 210)
  AUTHORS   Abraham,J.A., Whang,J.L., Tumolo,A., Mergia,A. and Fiddes,J.C.
  TITLE     Human basic fibroblast growth factor: nucleotide sequence, genomic
            organization, and expression in mammalian cells
  JOURNAL   Cold Spring Harb. Symp. Quant. Biol. 51 Pt 1, 657-668 (1986)
  MEDLINE   87217066
REFERENCE   5  (residues 1 to 210)
  AUTHORS   Story,M.T., Esch,F., Shimasaki,S., Sasse,J., Jacobs,S.C. and
            Lawson,R.K.
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TITLE Amino-terminal sequence of a large form of basic fibroblast growth factor isolated from human benign prostatic hyperplastic tissue
JOURNAL Biochem. Biophys. Res. Commun. 142 (3), 702-709 (1987)
MEDLINE 87156686
REFERENCE 6 (residues 1 to 210)
AUTHORS Kurokawa,T., Sasada,R., Iwane,M. and Igarashi,K.
TITLE Cloning and expression of cDNA encoding human basic fibroblast growth factor
JOURNAL FEBS Lett. 213 (1), 189-194 (1987)
MEDLINE 87162468
REFERENCE 7 (residues 1 to 210)
AUTHORS Sommer,A., Brewer,M.T., Thompson,R.C., Moscatelli,D., Presta,M. and Rifkin,D.B.
TITLE A form of human basic fibroblast growth factor with an extended amino terminus
JOURNAL Biochem. Biophys. Res. Commun. 144 (2), 543-550 (1987)
MEDLINE 87213238
REFERENCE 8 (residues 1 to 210)
AUTHORS Prats,H., Kaghad,M., Prats,A.C., Klagsbrun,M., Lelias,J.M., Liauzun,P., Chalon,P., Tauber,J.P., Amalric,F., Smith,J.A. and Caput,D.
TITLE High molecular mass forms of basic fibroblast growth factor are initiated by alternative CUG codons
JOURNAL Proc. Natl. Acad. Sci. U.S.A. 86 (6), 1836-1840 (1989)
MEDLINE 89184522
REFERENCE 9 (residues 1 to 210)
AUTHORS Feige,J.J., Bradley,J.D., Fryburg,K., Farris,J., Cousens,L.C., Barr,P.J. and Baird,A.
TITLE Differential effects of heparin, fibronectin, and laminin on the phosphorylation of basic fibroblast growth factor by protein kinase C and the catalytic subunit of protein kinase A
JOURNAL J. Cell Biol. 109 (6 Pt 1), 3105-3114 (1989)
MEDLINE 90078343
REFERENCE 10 (residues 1 to 210)
AUTHORS Shimoyama,Y., Gotoh,M., Ino,Y., Sakamoto,M., Kato,K. and Hirohashi,S.
TITLE Characterization of high-molecular-mass forms of basic fibroblast growth factor produced by hepatocellular carcinoma cells: possible involvement of basic fibroblast growth factor in hepatocarcinogenesis
JOURNAL Jpn. J. Cancer Res. 82 (11), 1263-1270 (1991)
MEDLINE 92091228
REFERENCE 11 (residues 1 to 210)
AUTHORS Shibata,F., Baird,A. and Florkiewicz,R.Z.
TITLE Functional characterization of the human basic fibroblast growth factor gene promoter
JOURNAL Growth Factors 4 (4), 277-287 (1991)
MEDLINE 92110035
REFERENCE 12 (residues 1 to 210)
AUTHORS Watson,R., Anthony,F., Pickett,M., Lambden,P., Masson,G.M. and Thomas,E.J.
TITLE Reverse transcription with nested polymerase chain reaction shows expression of basic fibroblast growth factor transcripts in human granulosa and cumulus cells from in vitro fertilisation patients
JOURNAL Biochem. Biophys. Res. Commun. 187 (3), 1227-1231 (1992)
MEDLINE 93038590
REFERENCE 13 (residues 1 to 210)
AUTHORS Patry,V., Bugler,B., Amalric,F., Prome,J.C. and Prats,H.
TITLE Purification and characterization of the 210-amino acid recombinant basic fibroblast growth factor form (FGF-2)

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  JOURNAL   FEBS Lett. 349 (1), 23-28 (1994)
  MEDLINE   94320639
REFERENCE   14  (residues 1 to 210)
  AUTHORS   Pantoliano,M.W., Horlick,R.A., Springer,B.A., Van Dyk,D.E.,
            Tobery,T., Wetmore,D.R., Lear,J.D., Nahapetian,A.T., Bradley,J.D.
            and Sisk,W.P.
  TITLE     Multivalent ligand-receptor binding interactions in the fibroblast
            growth factor system produce a cooperative growth factor and
            heparin mechanism for receptor dimerization
  JOURNAL   Biochemistry 33 (34), 10229-10248 (1994)
  MEDLINE   94347757
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Revised: October 24, 2001.

☐ 1: Science 1996 Feb 23;271 (5252):1116-20

Heparin structure and interactions with basic fibroblast growth factor.

Faham S, Hileman RE, Fromm JR, Linhardt RJ, Rees DC.

Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA 91125, USA.

Crystal structures of heparin-derived tetra- and hexasaccharides complexed with basic fibroblast growth factor (bFGF) were determined at resolutions of 1.9 and 2.2 angstroms, respectively. The heparin structure may be approximated as a helical polymer with a disaccharide rotation of 174 degrees and a translation of 8.6 angstroms along the helix axis. Both molecules bound similarly to a region of the bFGF surface containing residues asparagine-28, arginine-121, lysine-126, and glutamine-135, the hexasaccharide also interacted with an additional binding site formed by lysine-27, asparagine-102, and lysine-136. No significant conformational change in bFGF occurred upon heparin oligosaccharide binding, which suggests that heparin primarily serves to juxtapose components of the FGF signal transduction pathway.

PMID: 8599088 [PubMed - indexed for MEDLINE]